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Impact of massive dose of vitamin A given to preschool children with acute diarrhoea on subsequent respiratory and diarrhoeal morbidity

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Abstract

***Objective*—To assess the impact of vitamin A supplementation on morbidity from acute respiratory tract infections and diarrhoea.**

***Design*—Double blind randomised placebo controlled field trial.**

***Setting*—An urban slum area in New Delhi, India.**

***Subjects*—900 children aged 12-60 months attending a local health facility for acute diarrhoea of less than seven days' duration randomly allocated to receive vitamin A 200 000 IU or placebo.**

***Main outcome measures*—Incidence and prevalence of acute lower respiratory tract infections and diarrhoea during the 90 days after termination of the enrolment diarrhoeal episode measured by twice weekly household surveillance.**

***Results*—The incidence (relative risk 1·07; 95% confidence interval 0·92 to 1·26) and average number of days spent with acute lower respiratory tract infections were similar in the vitamin A supplementation and placebo groups. Among children aged 23 months or less there was a significant reduction in the incidence of measles (relative risk 0·06; 95% confidence interval 0·01 to 0·48). The incidence of diarrhoea was also similar (relative risk 0·95; 0·86 to 1·05) in the two groups. There was a 36% reduction in the mean daily prevalence of diarrhoea associated with fever in the vitamin A supplemented children older than 23 months.**

***Conclusions*—Results were consistent with a lack of impact on acute lower respiratory tract related mortality after vitamin A supplementation noted in other trials and a possible reduction in the severity of diarrhoea.**

Introduction

Clinical vitamin A deficiency as manifested by mild xerophthalmia predisposes to increased diarrhoea and respiratory morbidity.[1,2] The reported 20-54% reduction in mortality after vitamin A supplementation in preschool children in developing countries, however, seems larger than the maximal possible if the beneficial effect was restricted to the clinically vitamin A deficient population only.[3-5] Some of the observed benefit is postulated to be through correction of subclinical deficiency.[3,5,6] If this is true, then the impact of vitamin A supplementation on morbidity based on the prevalance of xerophthalmia would be an underestimate. There is thus a need to investigate the impact of vitamin A on morbidity directly.

Vitamin A supplementation, if focused on children seeking care for diarrhoea, would reach a substantial proportion of those clinically or subclinically deficient in vitamin A.[5] About two thirds of a large dose of vitamin A given to children with diarrhoea was shown to be absorbed and to cure clinical xerophthalmia.[7-9]

We conducted a trial to see whether 200 000 IU of vitamin A given to children aged 12-60 months with acute diarrhoea would reduce the incidence and severity of diarrhoea and lower respiratory tract infections during the subsequent three months.

Subjects and methods

The study was conducted at Govindpuri, an urban slum area in south Delhi with a population of 30 000. Men were most commonly employed as manual labourers. Few (5%) women worked outside the home. Almost all obtained drinking water from public hand pumps and used communal toilets. Health services were provided primarily by an adjacent government clinic and a few small private clinics. Vitamin A prophylaxis had not routinely been given to the study population in the preceding three years.

Children attending the government clinic were enrolled into the study if they were 12-60 months of age, if the duration of their diarrhoea was seven days or less, if their weight for height was 70% or more of the National Center for Health Statistics median, and if they resided in the slum area. Of the 1258 children with acute diarrhoea attending the clinic, 900 fulfilled the inclusion criteria and were enrolled. Among the remaining 358 children, the first identified reason for exclusion was: presence of signs and symptoms of vitamin A deficiency (30; 8·4%), had received a large dose of vitamin A in the past six months (29; 8·1%), was likely to migrate out of the study area (157; 43·9%), had associated systemic illness (82; 22·9%), had already been enrolled in the study within the preceding six months (28; 7·8%), had weight for height less than 70% of the National Center for Health Statistics median (4; 1·1%), and refused consent (28; 7·8%). Of the 30 excluded children with vitamin A deficiency, 16 had night blindness and 14 Bitot's spots. Among the 1258 eligible children, clinical vitamin A deficiency was seen in 13 (1·0%) at age 23 months or less, 67 (5·3%) at 24-36 months, and 40 (3·2%) beyond 36 months.

Informed consent was obtained and the selected children examined by a physician. Details were sought on the socioeconomic status of the family, characteristics of the enrolment illness, and feeding practices before the illness. The study was approved by the institutional ethics committee.

RANDOMISATION

Children were randomised to receive vitamin A

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200 000 IU or placebo. The randomisation code, using a simple randomisation scheme, was drawn up by the World Health Organisation, which supplied the vitamin A and placebo capsules labelled in accordance with the scheme. On enrolment the child was given the contents of a capsule with that serial number. If the child vomited within 30 minutes the second capsule with the same serial number was given.

SAMPLE SIZE ESTIMATES

The pretrial sample size estimate was based on detecting a 25% reduction in the prevalence of acute lower respiratory tract infection with 90% power and 5% significance by using a prevalence of 1·3 days of illness in 90 days. The variance used was 1·8, which was calculated by applying a 40% increase to the prevalence of 1·3 which would be assumed under the Poisson distribution in order to allow for between child heterogeneity in rates. This yielded a sample size of 358 children per group. We increased this by 25% and aimed for a trial size of 450 children per group to allow for attrition and lower than anticipated impact. This trial size was adequate to detect a 25% reduction in the incidence and prevalence of diarrhoea but not to detect a similar impact on the incidence of pneumonia, which required 609 children per group.

SURVEILLANCE

Household visits were made by a field assistant every three days during the enrolment episode and for 90 days after recovery. At each visit mothers were asked about cough since the last visit. If cough was present during the 24 hours before the current visit the respiratory rate was counted twice for one minute each and the child observed for lower chest indrawing. When the respiratory rate was 40 or more per minute it was measured at each subsequent visit till below this value at two consecutive visits. Mothers were asked about the frequency and characteristics of stools and other related signs.

When the child or a reliable attendant was not available repeat visits were made on two subsequent days. A recall period of only seven days was allowed.

All children with a respiratory rate of 35/min or more (suspected acute lower respiratory tract infection) were referred for a chest x ray examination immediately after the physician's examination. Agreement by two out of three radiologists was required for a diagnosis of pneumonia by using the WHO assessment form.[10]

Weight to the nearest 100 g and length or height to the nearest 0·1 or 0·2 cm were measured at enrolment and at the end of the study.

Serum vitamin A concentration was estimated before and a month after supplementation in 40 (5%) randomly selected children in each group, sufficient to allow detection of a 20% difference (SD 0·17 and 0·20) in mean post-supplementation serum vitamin A concentrations with 80% power and 95% confidence. Vitamin A concentrations were determined by high performance liquid chromatography by using a reversed phase column and water-methanol (ratio 5:95) eluant.[11]

TRAINING AND SUPERVISION

Field staff were trained in the measurement of respiratory rate, temperture, weight, height, and hydration status initially and at the end of each month. Weighing scales using standard weights and thermometers using water baths were standardised periodically. Reassessment was made by supervisors in one third of the morbidity recalls and measurements such as temperature, respiratory rate, and dehydration, and for half of the weight and length or height measurements by fieldworkers.

MEDICAL CARE

Treatment of diarrhoea, dysentery, and acute lower respiratory tract infection was strictly according to WHO recommendations. Symptomatic treatment for fever, scabies, and other minor ailments was dispensed to children attending the clinic.

ANALYSIS PROTOCOL AND STATISTICS

Diarrhoea was defined as the passage of three or more liquid stools in 24 hours. A diarrhoeal episode was classified as watery if the child passed three or more watery stools over 24 hours or more. Watery stools contained little faecal matter. Termination of a diarrhoeal episode was recorded when two or fewer liquid stools were passed per 24 hours over at least 48 hours, the second day of this period being the day of recovery.

The date of onset of acute lower respiratory tract infection was the first day when in addition to cough a respiratory rate of 40 or more per minute or lower chest indrawing was present. The day of recovery was the first of two consecutive household visits when the combination was no longer present. Two episodes of acute lower respiratory tract infection had to be separated by at least seven days without this combination. The diagnosis of clinical pneumonia was based on crepitations at auscultation in the presence of cough.

Out of 900 children, 58 were excluded from the final analysis—five for withdrawing consent, 46 for being unavailable or more than 30 study days, and seven because of persistent fast breathing for more than 45 days related to tuberculosis, cardiac disease, or severe anaemia. Of these 58 children, 30 were in the vitamin A supplementation group. Thus the final results are presented for 842 children, 422 in the vitamin A supplementation group and 420 in the placebo group.

Days at risk were estimated by subtracting the days of non-availability from the potential follow up of 90 days. Days at risk associated with ages 23 months or less and over 23 months were similarly estimated and used for age subgroup analysis.

The mean daily prevalence of diarrhoea and acute lower respiratory tract infection was estimated by calculating the prevalance rates for each child. Results were then averaged for the group. Asymptomatic days within episodes of pneumonia were not counted as positive days when calculating prevalence. The impact of vitamin A supplementation was also measured as relative risk for the incidence of morbidity in the vitamin A as compared with the placebo group, and 95% confidence intervals for the relative risk were estimated.[12]

Differences for continuous variables were evaluated by t test for normally distributed data. The Mann-Whitney U test was used for non-normal data. Bivariate variables were compared by χ^2 test or Fisher's exact test where appropriate. Vitamin A concentrations were compared by paired t test and 95% confidence intervals for differences in means estimated by methods for paired samples.[12]

Owing to a severalfold higher prevalence of vitamin A deficiency in children older than 23 months a stratified analysis of vitamin A impact by age (categorised as ≤ 23 months and > 23 months) was performed. A standard test of interaction[13] suggested the presence of a statistically significant interaction between age group and impact of vitamin A supplementation on both the incidence and prevalence of acute lower respiratory tract infection and diarrhoea.

Results

Age distribution, literacy status of mothers and fathers of the study children, family per capita

incomes, sources of water, and details of diarrhoeal episodes at enrolment were similar in the vitamin A and placebo groups (table I). Paired difference in mean serum vitamin A concentrations between baseline and one month after supplementation was 10·21 μg/dl (0·36 μmol/l) (95% confidence interval 3·54 to 16·88 (0·12 to 0·59); $P<0·001$) in 40 children tested in the vitamin A supplemented group and 3·58 μg/dl (0·12 μmol/l) (95% confidence interval −3·03 to 10·19 (−0·11 to 0·36); $P=0·136$) among the same number of children in the placebo group (table II).

Respiratory tract morbidity at ages 1-5 years—The overall impact of vitamin A on respiratory morbidity is summarised in table III. The incidences of acute lower respiratory tract infection in the vitamin A and placebo groups were similar. There were no significant differences in the mean prevalence rates for acute lower respiratory tract infections, cough, and lower chest indrawing. The incidence of measles per 90 day child period was 0·02 in the supplemented group and 0·05 in the placebo group (relative risk 0·54; 95% confidence interval 0·27 to 1·08). Subgroup analysis of children aged 23 months or less and over 23 months (tables III and IV) showed similar findings as in all trial children except for the incidence of measles, which was significantly reduced (relative risk 0·06; 95% confidence interval 0·01 to 0·48) in the vitamin A supplemented younger age group (table III).

Diarrhoea after supplementation—The incidence of diarrhoea per 90 day child period was 2·33 in the vitamin A group and 2·45 in the placebo group (relative risk 0·95; 95% confidence interval 0·86 to 1·05). There were no significant differences in the incidence of episodes lasting 14 days or more (relative risk 1·15; 0·70 to 1·80) or in the incidence of watery diarrhoea (relative risk 0·92; 0·78 to 1·07). In the age subgroup analysis the incidence rates of all diarrhoea, watery diarrhoea, and diarrhoea lasting 14 days or more were similar in the two groups. The mean daily prevalence of diarrhoea for all children and age subgroups is given in table V. There was a 36% reduction of diarrhoea with fever in the vitamin A supplemented children aged over 23 months.

TABLE I—*Comparison of initial socioeconomic and clinical characteristics of children supplemented with vitamin A or placebo*

Characteristic	Vitamin A group (n=451)	Placebo group (n=444)
Mean age (months) (SD)	26·9 (12·7)	26·3 (12·7)
No (%) of children aged:		
12-23 months	213 (47·2)	229 (51·6)
24-35 months	122 (27·1)	105 (23·6)
⩾36 months	116 (25·7)	110 (24·8)
No (%) male	231 (51·2)	233 (52·5)
Mean family per capita income in rupees per yer (SD)†	2262 (2442)	2135 (1043)
Parents who were literate:		
No (%) of mothers	84 (18·6)	85(19·1)
No (%) of fathers	279 (61·9)	282 (63·6)
Weight for height as % of National Center for Health Statistics median:		
No (%) >80%	377 (83·6)	375 (84·5)
No (%) 70-80%	74 (16·4)	69 (15·5)
No (%) who had received three doses of oral poliomyelitis and diphtheria-pertussis-tetanus vaccine	336 (74·5)	331 (74·5)
Enrolment diarrhoeal episode:		
Mean duration (days) (SD)	3·1 (1·7)	3·2 (1·7)
Mean stool frequency in 24 hours before admission (SD)	7·7 (3·3)	7·6 (3·3)
No (%) with fever	155 (34·4)	163 (36·7)
No (%) with vomiting	77 (17·1)	82 (18·5)

†49 Rupees=£1 (October 1994).
Differences between groups were non-significant throughout.

TABLE II—*Serum vitamin A concentrations initially and after supplementation with vitamin A or placebo in 5% sample of all children. Results expressed as numbers (percentages) of children*

Serum vitamin A		Vitamin A group (n=40)		Placebo group (n=40)	
μg/dl	θmol/l	Initial	After supplementation	Initial	After supplementation
⩽10	⩽0·35	6 (15·0)	3 (7·5)	5 (12·5)	4 (10·0)
11-20	0·38-0·70	6 (30·0)	3 (7·5)	7 (17·5)	6 (15·0)
21-30	0·73-1·05	12 (30·0)	12 (30·0)	13 (32·5)	7 (17·5)
31-40	1·08-1·40	6 (15·0)	10 (25·0)	9 (22·5)	14 (35·0)
⩾41	⩾1·43	4 (10·0)	12 (30·0)	6 (15·0)	9 (22·5)

Differences between groups were non-significant throughout.

TABLE III—*Incidence of acute respiratory tract infections and measles during 90 days after administration of vitamin A or placebo in all trial children*

Morbidity	No (%) in vitamin A group (per 90 day child period)	No (%) in placebo group (per 90 day child period)	Relative risk (95% confidence interval)
	All children		
No of child periods	410	409	
Acute lower respiratory tract infection	184 (0·44)	171 (0·41)	1·07 (0·92 to 1·26)
Pneumonia	76 (0·18)	79 (0·19)	0·96 (0·72 to 1·27)
Measles	12 (0·02)	22 (0·05)	0·54 (0·27 to 1·08)
	Age ⩽23 months		
No of child periods	179	195	
Acute lower respiratory tract infection	106 (0·59)	97 (0·49)	1·19 (0·99 to 1·43)
Pneumonia	47 (0·26)	36 (0·19)	1·35 (0·92 to 1·96)
Measles	1 (0·005)	17 (0·08)	0·06 (0·01 to 0·48)
	Age >23 months		
No of child periods	231	214	
Acute lower respiratory tract infection	78 (0·33)	74 (0·34)	0·98 (0·75 to 1·26)
Pneumonia	29 (0·12)	41 (0·23)	0·66 (0·42 to 1·02)
Measles	11 (0·04)	5 (0·02)	2·04 (0·72 to 5·77)

Discussion

In this study vitamin A supplementation in children resulted in a significant decline in measles morbidity, but there was no such impact on the incidence or prevalence of cough and acute lower respiratory tract infection. The prevalence of diarrhoea with fever was reduced in the older vitamin A supplemented children.

This lack of a significant impact on respiratory morbidity is in contrast with the findings of a positive association of cough and lower respiratory tract infections with vitamin A deficiency in several observational studies.[1 2 14-16] It is, however, consistent with the lack of impact on deaths from pneumonia in nearly all vitamin A supplementation trials in children in which there was a significant decline in all cause mortality.[5 17 18]

An impact on the severity of diarrhoea was observed for only one of the several parameters evaluated in the age subgroup analysis. This was unexpected, as a reduction in diarrhoea related mortality has been reported in several vitamin A trials in children of 1-5 years of age.[5 14 16-18] Other studies have also not found a significant decrease in the incidence or prevalence of diarrhoea, although a study in Ghana, where vitamin A deficiency is widely prevalent, reported a decrease in vomiting and diarrhoea recorded during physician visits in vitamin A supplemented children.[18] Probably vitamin A does have an impact on the severity of diarrhoea but active surveillance for accurate morbidity measurements limits our ability to detect it. In this study, for example, intensive household surveillance resulted in early and efficient treatment of dysentery, of associated systemic infection, and treatment with oral rehydration salts for all episodes.

A significant decline in measles incidence in the vitamin A group aged below 23 months and a similar trend in the older children was consistent with the reduced measles mortality and severity noted in other studies.[19 21] Overall, these findings are consistent with the view that the most profound morbidity effects of vitamin A supplementation may be measles related.[22] Though a direct impact on pneumonia morbidity was not observed, reduced measles incidence and severity would be expected to have a favourable impact on respiratory morbidity associated with measles.

Recent studies have found an increased prevalence of acute lower respiratory tract infections after vitamin A supplementation.[23 24] This may be due to the possible

TABLE IV—*Mean daily prevalence of acute respiratory tract infections during 90 days administration of vitamin A or placebo in all trial children*

Morbidity	Vitamin A group	Placebo group	Ratio of vitamin A to placebo	P value
	All children			
Acute lower respiratory tract infection	0·0405	0·0337	1·20	0·66
Cough irrespective of other features	0·2744	0·2588	1·06	0·23
Lower chest indrawing	0·0032	0·0018	1·77	0·17
	Age ≤23 months			
Acute lower respiratory tract infection	0·0720	0·0507	1·42	0·31
Cough irrespective of other features	0·2766	0·2588	1·06	0·17
Lower chest indrawing	0·0047	0·0066	0·71	0·13
	Age >23 months			
Acute lower respiratory tract infection	0·0251	0·0286	0·87	0·92
Cough irrespective of other features	0·2688	0·2600	1·03	0·85
Lower chest indrawing	0·0027	0·0027	1·00	0·90

TABLE V—*Mean daily prevalence of diarrhoea during 90 days after administration of vitamin A or placebo*

Morbidity	Vitamin A group	Placebo group	Ratio of vitamin A to placebo	P value
	All children			
Diarrhoea	0·1011	0·1042	0·97	0·64
Watery diarrhoea	0·0104	0·0103	1·00	0·23
Diarrhoea plus fever	0·0141	0·0147	0·95	0·35
	Age ≤23 months			
Diarrhoea	0·1044	0·1050	0·99	0·80
Watery diarrhoea	0·0130	0·0115	1·13	0·25
Diarrhoea plus fever	0·0192	0·0144	1·33	0·43
	Age >23 months			
Diarrhoea	0·0844	0·0877	0·96	0·47
Watery diarrhoea	0·0073	0·0077	0·95	0·62
Diarrhoea plus fever	0·0085	0·0133	0·64	0·05

immunosuppressive effect of vitamin A excess,[25 26] as shown convincingly in studies of vitamin A deficiency.[25-27] These findings have led to the postulation that supplementation with large doses of vitamin A in replete infants may increase serum and tissue vitamin A to excess concentrations with the possibility of side effects while simultaneously offering benefit through improved vitamin A status in severely deficient infants.

The issue of whether vitamin A supplementation may increase acute lower respiratory tract infection in some settings needs to be clarified, given the suggestion of vaccination linked supplementation in early infancy.[28] Given the high incidence of acute lower respiratory tract infection at this age even a small increase in risk could represent a large population impact.

We did not find a significant increase in the incidence or prevalence of lower respiratory tract infection, clinical pneumonia, or cough in the vitamin A supplemented children. However, on the basis of our data we cannot altogether exclude this possibility, as the mean daily prevalence of acute lower respiratory tract infections was 42% higher in the vitamin A supplemented children under 23 months of age in whom the prevalence of vitamin A deficiency was low. Further research on this issue is warranted.

Future trials of much larger size should include assessment of initial vitamin A status to allow analysis of the morbidity impact of vitamin A supplementation in vitamin A replete infants as well as in deplete infants. These studies should also dissociate the impact on cough from that on pneumonia.

Meanwhile, given the significant reduction in mortality after vitamin A supplementation in children of 6 months to 5 years of age in several trials, supplementation should be provided at these ages in settings where vitamin A deficiency is a public health problem.

Public health implications

- In developing countries subclinical vitamin A deficiency is common
- Subclinical vitamin A deficiency is believed to increase the risk of common infections like measles, diarrhoea, and pneumonia
- This study shows that in children aged 1-5 years vitamin A supplementation reduces the prevalence of diarrhoea associated with fever by 36%
- The children given supplements also suffered less measles, but there was no impact on pneumonia

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